Remarks

Information Disclosure Statement

With respect to the "PCT International Search Report dated 09/23/1998 for PCT Application No. PCT/EP98/03182" and the "PCT International Search Report dated 09/23/1998 for PCT Application No. PCT/EP98/03182" in the submitted PTO 1449, Applicants point out that these documents were sent to clarify to the Examiner that some of the documents that were cited in the PTO 1449 were also mentioned in an International Search Report. Applicants wish to point out that the documents that were mentioned on the International Search Report, i.e. WO 97/21701, as well as the Indolfi *et al.* article and the Irani *et al.* article, were cited in the Form 1449 also.

Claim rejections – 35 USC § 112

Claims 20 –27 are rejected under 35 U.S.C. § 112. The Examiner states that the specification does not reasonably provide enablement for "a stereoisomeric form thereof". (Office Action dated August 10, 2006 at page 2.) Applicants respectfully disagree with this allegation.

The term "stereoisomeric forms" or "stereoisomers" covers two different classes of isomers. Applicants refer to "Introduction to Organic Chemistry, Third edition (1985), Macmillan Publishing Company, by A. Streitwieser, Jr and C. Heathcock", page 124, line 22 –28 (copy of said page is enclosed), which states:

> "*Compounds that are stereoisomers of one another, but are not enantiomers, are called diastereomers and are said to have a diastereomeric relationship. The stereoisomeric relationships for a compound having two unlike stereocenters are summarized in schematic form in Figure 7.10.*

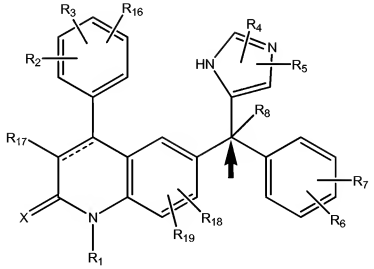
In general, the maximum number of possible stereoisomers for a compound having n stereocenters is given by 2^n. Thus for a compound with one stereocenter, there are 2^1 = 2 stereoisomers. ..."

The Examiner alleges:

"*The claims are very broad due to the vast number of possible compounds of [sic] that are described as being "a stereoisomeric form thereof". The instant claims cover "stereoisomeric form"[sic] of formula (I) that are known to exist and those that may be discovered in the future, for which there is no enablement provided.* "

(Office Action dated August 10, 2006 at page 4, line 14 to line 18.)

Applicants respectfully disagree with this statement. The compounds as depicted by Formula (I) only have one stereogenic center, indicated by the arrow in the figure hereunder.



As is explained in the quote from Streitwieser et al., this means that there can only be two enantiomers for each given formula. Applicants are aware that by introducing certain substituents the number of stereoisomers can increase, but Applicants contend that as a general matter a person skilled in the art would not consider this structure as giving rise to an unreasonable number of compounds encompassed in the claim *"due to the vast number of possible compounds that are described as being "a stereoisomeric form thereof""*. Applicants further submit that given the mathematical relationship between the number of stereocenters in a molecule (which is a fixed number) and the number of stereoisomers, there are no stereoisomeric forms "*that may be discovered in the future*."

The Office Action states on page 5, line 2 –11:

> *"...Although some optical isomers are made by simple isolation procedure, many stereoisomers of drug(s) requires high level of skill in separating, quantitating [sic] and predicting the pharmacokinetic and biological characteristics of each isomer (see Anal Biochem, 1988, 9; 168(2):398-404). Therefore, without sufficient guidance from the instant specification how to make, quantitate and determine the pharmacokinetic and biological activity of "stereoisomeric form" of formula (I), the skilled artisan would have to undergo an undue amount of experimentation to make the claimed product encompassed by the instant invention.*

(Office Action dated August 10, 2006 at page 5, line 2 –11.)

Applicants respectfully disagree with this statement. The issue at hand is whether the guidance given to separate the stereoisomers from the mixtures is enough to enable a person skilled in the art to make the (pure or substantially pure) stereoisomers. As will be shown hereunder, it is the Applicants opinion that persons skilled in the art were sufficiently knowledgeable about separating stereoisomers in general and specifically enantiomers.

First, a distinction needs to be made between enantiomers and diastereomers. With respect to diastereomers, Applicants refer to "Stereochemical Terms and Concepts" in the book "Drug Stereochemistry, Analytical Methods and Pharmacology", second Edition, Revised and Expanded, edited by Irving Wainer, published in 1993 on page 29, third paragraph for an explanation of the properties of diastereomers (copy attached).

> ***"B Diastereomers***
>
> *Diastereomers are optical isomers that are not related as an object and its mirror image. Unlike enantiomers, the physical and chemical properties of diastereomers can differ and it is not unusual for them to have different melting and boiling points, refractive indices, solubilities, etc. Their optical rotations can differ in both sign and magnitude."*

As stated above, diastereomers are as different from each other as other structural analogues and the different physical and chemical properties allow for a separation that is known in the art.

To prepare one of the enantiomers separately there are fundamentally two options: either one synthesizes the enantiomer in a stereoselective manner or one synthesizes the enantiomer in a non-selective manner and then separates the resulting racemic mixture. Hence in the non-stereoselective manner there is the step of synthesis and then the step of separation. Applicants will first establish the level of enablement that needs to be described in the patent specification and then Applicants will show that both steps, i.e. the synthesis step as well as the separation step, are sufficiently exemplified and that there is sufficient guidance to enable the term "stereoisomer form thereof".

Applicants submit that the description of the appropriate standard for enablement can be found in the Manual for Patent Examining Procedure, that states that it is preferred not to

mention what is already known in the art. See MPEP Eight Edition Incorporating Revision No 4. Page 2100-193, column 1, line 25 to line 30 (emphasis added):

> *"("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation") A patent need not teach, and preferably omits, what is well know in the art."*

Applicants further submit that "[*e*]*nablement is determined from the viewpoint of persons of skill in the field of the invention at the time the patent application was filed".* (Ajinomoto Co, Inc. v Archer-Daniels-Midlands Co, 228 F.3d 1338, 56 USPQ2d 1332 (Fed Cir 2000)).

The present application was filed as a PCT application on May 25, 1998 with a priority claim to a provisional application filed on June 2, 1997. Consequently the relevant date to take into account for establishing what the person skilled in the art would know is June 2, 1997. (Office Action dated August 10, 2006 at page 5, line 2 –11.)

The Examiner alleges that the person skilled in the art would have to undertake an undue amount of experimentation to make the claimed products. (Office Action dated August 10, 2006 at page 5.) The Examiner alleges this on the basis that there is no sufficient guidance from the instant specification to make the claimed products. (Office Action dated August 10, 2006 at pages 4-5.) The Examiner bases his contention on an article of 1988. Id.

Applicants submit with all due respect that said article does not reflect the state of the art of separating stereoisomers in 1997, which is the relevant date as shown above. Applicants submit that the art of stereoisomer separation was sufficiently evolved in 1997 not to require an extensive explanation of all the possible techniques that can be used to

separate the stereoisomers. Indeed, the Manual for Patent Examining Procedure prefers that the application does not mention what the person skilled already knows. To properly reflect the state of the art of separating enantiomers, Applicants want to refer, for example, to Chapter 6 from the Book "Drug Stereochemistry, Analytical Methods and Pharmacology, Second Edition, Revised and Expanded, edited by Irving W Wainer, and published by Marcel Dekker, Inc. which was published in 1993 (still four years before the filing date of this application). This Chapter is entitled: HPLC Chiral Stationary Phases For The Stereochemical Resolution of Enantiomeric Compounds, The current state of the art" by Irving Wainer. (A copy of said chapter is enclosed). The Introduction reads as follows on page 139 (emphasis added):

> *In the first edition of this work, the conclusion of this chapter stated The HPLC chiral stationary phases (CSPs) that are already available, and those that will shortly be on the market will play a large role in future regulatory and pharmacological applications, and the last half of the 1980s should see the continued rapid expansion of the use of HPLC-CSPs. By the end of the decade, these columns should be a routine analytical tool in most analytical, regulatory, and pharmacological laboratories."*

In other words, one of the techniques that are specifically mentioned in the patent application, i.e. liquid chromatography using a chiral stationary phase is mentioned in the literature in 1993 (four years before the filing of the present application) as a routine analytical tool. Hence Applicants are of the opinion that there was sufficient knowledge amongst persons skilled in the art to separate enantiomers or stereoisomers in general.

Applicants further point to the specification as filed (page 16, line 11 to line 25) for general guidance and direction with respect to other methods as well:

> *"The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be*

separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated there from by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials."

Furthermore, Applicants submit that there are specific examples showing how to make the pure stereoisomers disclosed in the specification as filed. The Examiner's attention is drawn towards Example B.8 (page 29, line 26 to page 30, line 15) wherein the preparation of compound 23, compound 24, compound 74 and compound 75 are clearly explained. Moreover, when having a closer look at the actual Example B.8, the Examiner will note that the method used there is a standard chromatographic separation over a chiral column, a technique already well know at the time. Although this is clearly not the only technique that could be used, it is a technique that is widely available and would be applicable to most, if not all, of the compounds.

With respect to "quantitating biological activities" (see Office Action dated August 10, 2006 at page 5, line 4), Applicants refer to the Pharmacological Example that describes a very straightforward manner for quantitating the smooth muscle cell proliferation effect of test compounds. Applicants submit that for a person or ordinary skill in the art of pharmacological research, setting up this test and running the test does not amount to undue experimentation. Moreover, the Applicants submit that once the enantiomers are

separated there is no intrinsic difficulty in testing enantiomers or any stereoisomer that would make the testing of stereoisomers more difficult than the testing of any other type of compound.

In view of the above-mentioned facts and arguments, it is the Applicant's position that the person skilled in the art would not be forced to undue experimentation in view of the "stereoisomers" being claimed as part of the invention. Accordingly, Applicants respectfully request the Examiner to withdraw his rejection on 35 USC § 112.

Double patenting rejection

Claims 20-27 are rejected under the judicially created doctrine of double patenting over claims 1-5 of U.S. Patent No. 6,743,805. (Office Action dated August 10, 2006 at page 6.)

Please find enclosed a terminal disclaimer. Applicants are of the opinion that with this submission the double patenting rejection should be obviated. Accordingly, Applicant requests withdrawal of the aforementioned double patenting rejection of claims 20-27.

Conclusion

Early favorable action on the merits is respectfully requested.

Applicant respectfully requests that a timely Notice of Allowance of claims 20-27 be issued in this case.

The Commissioner is hereby authorized to charge Deposit Account No. 10-0750/JAB1680Div3/AGK for the Terminal Disclaimer Fee required under 37 CFR 1.20(d). No additional fees are believed due. However, the Commissioner is hereby authorized to charge any additional fees or deficiencies due or credit any overpayment to Deposit Account No. 10-0750/JAB1680Div3/AGK.

Respectfully submitted,

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